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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,193	12/21/2005	Heinrich Haas	062587-5003	6810

9629 7590 03/17/2009

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
4121	

MAIL DATE	DELIVERY MODE
03/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,193	HAAS ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *24-59* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 24-33 and 54, drawn to a composition comprising camptothecin associated with a cationic polymer.

Group II, claims 36-50, drawn to a colloidal nanoaggregate.

Group III, claims 52-53, drawn to a method of producing a colloidal nanoaggregate.

Group IV, claims 51, 55-59, drawn to a method of treating a disease.

As set forth in Rule 13.1 of the Patent Cooperation Treaty (PCT), "the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept." Moreover, as stated in PCT Rule 13.2, "where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." Furthermore, Rule 13.2 defines "special technical features" as "those technical features that define a

contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Groups I-IV is a mixture comprising camptothecin in its carboxylate form with an organic cationic molecule. The mixture of claim 24 does not present a contribution over the prior art. As disclosed in Ray et al. (Document N on the PTO-892) in view of Yang et al. (Document V on the PTO-892), the mixture of instant claim 24 does not involve an inventive step.

Ray et al. (Document U on the PTO-892) (hereafter referred to as Ray) teaches, in Figures 2 and 3, that both camptothecin and polyamines are useful for promoting apoptosis. Ray shows this by showing that apoptosis decreases upon addition of an inhibitor of camptothecin. Ray further shows, in Figure 8, that a composition comprising both camptothecin and the cationic polymer diethylglyoxal bis-(guanylhydrazone) induces more apoptosis than just camptothecin by itself.

Ray does not read on a composition comprising camptothecin that is essentially free of the lactone form.

Yang et al. (Document V on the PTO-892) teaches, on page 751, left column, top, a composition wherein camptothecin is added to ammonium hydroxide, an alkaline compound. Addition of an alkaline compound causes the camptothecin to change from

a lactone form to a carboxylate form, as of page 751, right column, "Introduction" section of Yang.

Neither Yang nor Ray teaches that the molar ratio of the organic cationic molecule to camptothecin is at least 1:1. However, according to MPEP 2145.05(II), differences in concentration will not support the patentability of subject matter unless there is evidence indicating that such a concentration or temperature is critical.

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the inventions of Ray and Yang. This is because, according to Yang, page 751, right column, the lactone form of camptothecin

is not water soluble, whereas the carboxylate form is water soluble. Hence, one of ordinary skill in the art would have used a water soluble form of camptothecin for biotic administration.

It is noted in MPEP 2144.06, that combining two equivalents known for the same purpose to form a third composition results in an obvious composition. In the instant case, it was already known in the art that camptothecin causes apoptosis, and already known in the art that polyamines cause apoptosis. Hence, a composition combining said components in order to cause apoptosis of cancer cells results in a case of prima facie obviousness. See the following from MPEP 2144.06

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

As such, Group I does not share a special technical feature with the instant claims of Group II, III, and IV. Therefore, the claims are not so linked within the meaning of PCT Rule 13.2 so as to form a single inventive concept, and unity between Groups I-III is broken.

Election of Species

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

- The species are as follows:

- If Group I is elected, EACH of the following species elections are required:

    - *Cationic amphiphile* (e.g. lipid, lysolipid etc.) with claim 26 reading upon this species.

    - *Group Present on cationic amphiphile* (e.g. tertiary amino or quaternary ammonium) with claims 27-29 reading upon this species.

    - *Cationic Polymer* (e.g. polyelectrolyte, an acid of a polyallylamine, a polyamine etc.) with claim 30 reading upon this species.

    - *Anionic/Neutral amphiphile* (e.g. sterol or lipid etc.) with claims 32-35 reading upon this species.

    - *Sterol* (e.g. cholesterol) with claim 33 reading upon this species. This election required is sterol is chosen for claim 32.

    - *Lipid* (e.g. lysolipid, lysophospholipid, sphingolipid etc.) with claims 34 and 35 reading upon this species. This species election required if "lipid" is elected as of claim 32.

- If Group II is elected, EACH of the following species elections are required:
    - *Anionic/Neutral amphiphile* (e.g. sterol or lipid etc.) with claims 39-42 reading upon this species.
    - *Sterol* (e.g. cholesterol) with claim 40 reading upon this species.
    - *Lipid* (e.g. phospholipid, lysolipid, sphingolipid etc.) with claim 41-42 reading upon this species. This species election must completed if the species "lipid" is elected for claim 39.
    - *Nanoaggregate* (e.g. emulsion droplet, micelle, liposome etc.) with claim 46 reading upon this species.
    - *Cryoprotectant* (sugar, alcohol, trehalose, maltose etc.) with claim 48-49 reading upon this species. Applicant must elect one sugar, one alcohol, or a combination of one specific sugar and one specific alcohol.
- If Group III is elected, EACH of the following species elections are required:
    - *Method of forming nanoaggregate* (e.g. homogenization, a lipid film, a solvent injection procedure) with claim 52 reading upon this species.
- If Group IV is elected, EACH of the following species elections are required:
    - *Disease with enhanced angiogenic activity* (e.g. cancer, inflammatory diseases, rheumatoid arthritis etc.) with claims 56-59 reading upon this species.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. As to the claims present, Applicant is required to elect a single term from the possibilities recited by the claims. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

- The following claims are generic:
    - Claims 24-25, 31, and 54 as to Group I
    - Claims 36-38, 43-45, and 50 as to Group II.
    - Claim 52 as to Group III.
    - Claims 51 and 55 as to Group IV.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

Each chemical species is a distinct chemical which lacks a special technical feature in view of Weiner (US Patent 5,200,393) column 3 lines 25-35.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the

prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Joint Inventors and Rejoinder

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to

be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on Monday - Thursday 7:30AM - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/I. S./
Examiner, Art Unit 4121

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121